DETAILED ACTION

The present Office Action is responsive to the Amendment received on December 16, 2008. Claims 1, 2, 5-12, 14-26, and 37-59 are pending and are under prosecution.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 2, 5-12, 14-26, and 37-59 under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (U.S. Patent No. 5,922,591, issued July 13, 1999) in view of Waller et al. (Applied Environmental Microbiology, 2000, vol. 66, no. 9, pages 4115-4118) as evidenced by Hassibi et al. (US 2004/0197845 A1, published October 7, 2004), made in the Office Action mailed on October 8, 2008 is withdrawn in view of the Amendment.

Specifically, Applicants' arguments stating that Hassibi et al. is not prior art is found persuasive.

Rejection - New Grounds

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5-12, 14-26, and 37-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (U.S. Patent No. 5,922,591, issued July 13, 1999) in view of Waller et al. (Applied Environmental Microbiology, 2000, vol. 66, no. 9, pages 4115-4118) as evidenced by Bjornson et al. (U.S. Patent No. 6,103,199, issued August 15, 2000).

Anderson et al. disclose a target detection system, said system comprising:

a) a PCR chamber (column 2, lines 24-27; column 3, lines 33-37; column 9, lines 8-11);

b) a capillary electrophoresis (CE) mechanism (column 15, lines 33-38), and microchannels connecting various chambers (column 2, lines 35-40), wherein the fluid flow is controlled by pneumatically controlled valves (column 4, lines 55-56; column 29, lines 53-54).

With regard to claims 2 and 12, Anderson et al. disclose that their DNA analysis mechanism comprises PCR and CE (discussed above), wherein the artisans explicitly disclose that, "[m]icrocapillary array electrophoresis generally provides a rapid method for size based sequencing, PCR product analysis.." (column 15, lines 46-48).

With regard to claim 5 and 10, the chamber for PCR is disclosed as being used for amplification of DNA obtained from lysing the target of interest (column 6, lines 30-48).

With regard to claims 6 and 14, the capillary is etched microchannel (column 15, lines 63-67).

With regard to claims 7 and 15, the artisans also disclose the necessary step of desalting or purifying the extracted DNA (column 7, lines 17-36).

With regard to claims 23 and 24, the device chamber is formed on a glass layer (column 18, lines 60-63).

With regard to claim 25, the device disclosed by Anderson et al. comprises a plurality of channels (Figure 12C).

With regard to claims 26, 39, 43, 47, and 51, the pneumatic valves are controlled by vacuum (column 29, lines 54-57).

With regard to claims 38, 42, 46, and 50, the target is contemplated as being pathogens (column 6, line 33).

With regard to claims 41, 45, 49, and 53, the artisans employ their valves to direct the fluid directions (see Figure 12C, valves 1262, 1264, 1266, and 1268).

While Anderson et al. explicitly contemplate a microfluidic device which couples both PCR and CE analyses, the artisans are not explicit in stating that their device is adapted for conducting immunocapture (claims 1, 8, 9, 11, 16-22, 37, 40, 44, 48, and 52).

Anderson et al. do not explicitly teach an immunocapture chamber wherein said immunocapture chamber comprises immobilized capture reagents, solid phase capture particles therein, backed bed of beads, magnetically confined beads.

Waller et al. disclose a method of immunocapture PCR assay for the purpose of detecting a pathogenic species, *Campylobacter jejuni* from food samples (see Abstract).

Waller et al. explicitly disclose a step of binding *Campylobacter* in sample by adding polyclonal anti-*Campylobacter jejuni* IgG to the sample, followed by the purification of the antigen-antibody complex with anti-rabbit IgG-coated Dynabeads (page 4116, 1st column, 1st paragraph).

Waller et al. also disclose the step of lysing the captures cells, so as to remove the *C. jejuni* genomic DNA from the antigen-antibody complex, followed by the amplification of said genomic DNA in a PCR reaction (page 4116, 1st column, 2nd and 3rd paragraph).

Waller et al. evidences the well known practice of cleaning up and concentrating the isolated DNA prior to amplification procedure (page 4116, 1st column, 2nd column).

Bjornson-1 discloses a microfluidic device which is configured to conduct variety of assays, such as, "immunoassays, DNA binding assays, ..." (column 10, lines 29-31).

In particular, Bjornson-1 discloses:

> "Alternatively, ***selected components may be guided to channels filled with specific binding members, such as antigen-antibodies***, reactive with given substances of interest being moved in the medium or moved into contact with complementary components having a label or other member of a signal producing system of other types of chemicals for any number of purposes such as various transformations that are either physical or chemical in nature. ***Furthermore, bacterial or mammalian cells, or viruses may be sorted by complicated microfluidic networks*** in connection with a plurality of electrodes capable of

> generating electrical potentials of a variety of different strengths in order to move the cells or viruses through the fields based on the size, charge or shape of the particular material being moved. ***Separated cells or viruses may be analyzed or modified subsequently***. For example, cell fractionation is possible by employing solid-phase extraction materials, including paramagnetic beads, non-magnetic particles, or the like to specifically bind with the desired cells such that the bead-cell complex can be separated from the other cells. ***Cell lysis is then possible for releasing the intracellular materials for further analysis."*** (column 13, lines 36-56)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Anderson et al. with the teachings of Waller et al. and Bjornson et al., thereby arriving at the invention as claimed for the following reasons.

Initially, the use of microfluidic device has been well-established in the art, the benefits of which would be certainly recognized by one of ordinary skill in the art, such as being able to conduct series of biological reactions on a single device, resulting in efficiency, reduced chances of contamination, human errors, etc.

This advantage is evidenced by Bjornson et al.:

> "The so-called 'lab-chip' technology enables ***sample preparation and analysis to be carried out onboard microfluidic based cassettes. Moving fluids through a network of interconnecting enclosed microchannels of capillary dimensions*** is possible using electrokinetic transport methods." (column 3, lines 23-26)

Additionally, the use of such microfluidic device for the purpose of detecting various target nucleic acids from a sample, be it for a certain medical condition (i.e., cancer) or for the presence of pathogens from samples, is also well known and recognized in the art of miniaturized biological device.

Whether one of ordinary skill in the art, at the time the invention was made would have been motivated to combine the teachings of Anderson et al. with the teachings of Waller et al. is the question in the present formulation of obviousness. It is respectfully submitted that one of ordinary

skill in the art would have been certainly motivated to combine the teachings for the following reasons.

As previously stated, Anderson et al. disclose a microfluidic device, which is capable of amplifying and conducting electrophoresis of the amplified products

However, the amplification method employed by Anderson et al. is drawn to a PCR amplification, which has recognized deficiencies when it comes to the detection of pathogens, one of which is clearly and explicitly identified by Waller et al.:

> "Due to the prevalence of *Campylobacter* species in the food supply, routine and reliable monitoring for these pathogens is necessary in order to reduce their impact upon human health. Cultivation methods involving enrichment, isolation, and biochemical characterization require 4 to 5 days to complete…Due to the perishable nature of many food items, a more rapid detection method is necessary to feasibly monitor the potential sources of theses pathogens. For this reason, we have developed an immunocapture PCR method for the detection of *Campylobacter* in foods." (page 4115, 1st column, bottom paragraph)

Therefore, the motivation to conduct immunocapture PCR was ***clearly present in the art.***

The question to be answered is whether one of ordinary skill in the art would have had a reasonable expectation of success at combining the immunocapture module into a "microsized" device, such as the microfluidic device of Anderson et al., arriving at the invention as claimed.

To this end, it is respectfully submitted that Bjornson et al. clearly evidences that such can be done.

As discussed previously, Bjornson et al. clearly evidences to an ordinarily skilled artisan that a microfluidic device can be manufactured to comprise a module which allows for antigen-antibody binding, pathogen-binding, sorting, and their disruption for further analysis (see above).

While Bjornson et al. generally disclose that selected components can be guided to a channel with specific binding pairs such as antigen-antibodies, Bjronson et al. are not explicit in stating that pathogens be captured via immunocapture process (i.e., antigen-antibody binding).

However, such teaching was already provided for by Waller et al.

The question is whether one of ordinary skill in the art would have had a reasonable expectation of success at providing a chamber which allows for antigen-antibody binding (whether it be for pathogen detection or not), and this question has been answered by Bjornson et al. who explicitly state that a microfluidic device can be tailored to comprise a miniaturized chamber allowing for antibody-antigen binding.

In addition, Bjornson et al. also explicitly contemplate their microfluidic device also comprising capillary electrophoretic analysis module:

> "Capillary-based separation are widely used for analysis of a variety of analyte species. Numerous techniques, all based on electrokinetic-driven separations, have been developed. Capillary electrophoresis is one of the more popular of these techniques and can be considered to encompass a number of related separation techniques ..." (column 3, lines 60-65; Bjornson et al.)
> "Currently, sophisticated experiments in chemistry and biology, particularly molecular biology, involve evaluating a large numbers of samples. For example, DNA sequencing of genes is time consuming and labor intensive. In the mapping of the human genome, a researcher must be able to process a large number of samples on a daily basis. If capillary [electrophoresis] can be conducted and monitored simultaneously on many capillaries, i.e., multiplexed, the cost and labor for such projects can be significantly reduced. Attempts have been made to sequence DNA in slab gels with multiple lanes to achieve multiplexing. However, slab gels are not readily amenable to high degree of multiplexing and automation ... Capillary electrophoresis possesses several characteristics which makes it amenable to this application [multiplexing and automating]." (column 4, lines 22-34 and 47-48; Bjornson et al.)

Provided with such teachings, one of ordinary skill in the art at the time the invention was made would have had a clear expectation of success at combining the immunocapture chamber coupled to the PCR and CE mechanism of Anderson et al.

To reiterate, given the motivation provided for by Waller et al., which allows one of ordinary skill in the art to detect pathogens in a sample, wherein the artisans explicitly disclose the uses of antibody and bead assisted immunocapture of pathogens, followed by the lysis of the captured pathogens prior to amplification, one of ordinary skill in the art would have had a reasonable expectation of success at creating a chamber or chambers prior to the PCR-CE detection on the microfluidic device of Anderson et al. as clearly evidenced by Bjornson et al.

Lastly, with regard to providing preconcentration and clean chambers in the device of Anderson et al., it would have been obvious in view of the fact that Waller et al. explicitly disclose the step of cleaning up and concentrating the DNA prior to its amplification. In addition, such practice would have been well within the purview of an ordinarily skilled artisan given the fact that PCR would have been more effective by removing the contaminating cell contents when lysing the pathogens in the sample.

In *KSR International Co v. Teleflex Inc*, the supreme court stated that, "A person of ordinary skill in the art is also a person of *ordinary creativity*, not an automation" (82 USPQ2d at 1397) and that "in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle" and take into account, "the inference and creative steps that a person of ordinary skill in the art would employ" (82 USPQ2d at 1396).

Clearly, given the art's motivation to combine immunocapture with PCR analysis, and the teaching in the art which enables a one of ordinary skill in the art to provide a immunocapture chamber in a miniaturized device (i.e., microfluidic device), one of ordinary skill in the art would have been able to, "fit the teachings of multiple [disclosures] together like pieces of a puzzle," arriving at the claimed invention.

Lastly, it is respectfully submitted that such "fitting" of the teachings would not have been "beyond [the] ... skill [level]" of one of ordinary skill in the art

In *KSR*, the supreme court stated:

> "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious **unless its actual application is beyond his or her skill**." (page 13, emphasis added).

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 9:00 a.m. to 5:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be

sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
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Art Unit 1637
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/YJK/